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(54) Title: INTEGRATED OPTICAL MOLECULAR DETECTION DEVICE AND METHOD THEREFOR

(57) Abstract

A substrate (12) defines a binding site (14) for receiving a molecular receptor (16). A light source (18) and an optical detector (20) are incorporated in the substrate (12). The light source (18) illuminates the binding site (14) through the substrate (12) to produce an optical indication of a molecule (19) hybridized to the molecular receptor (16). The optical detector (20) detects the optical indication through the substrate (12). Preferably, the substrate (12) defines a first side on which the binding site is defined, and a second side opposite the first side on which the light source and the optical detector are integrated. A transparent electrode can be included at the binding site for field-assisted hybridization and de-hybridization.

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INTEGRATED OPTICAL MOLECULAR DETECTION DEVICE AND METHOD THEREFOR

Field of the Invention

The present invention relates to optical molecular detection devices and methods of detection therefor.

Background of the Invention

Recently, an increased effort has been directed toward the development of chips for molecular detection. In general, a molecular detection chip includes a substrate on which an array of binding sites is arranged. Each binding site (or hybridization site) has a respective molecular receptor which binds or hybridizes with a molecule having a predetermined structure. A sample solution is applied to the molecular detection chip, and molecules in the sample bind or hybridize at one or more of the binding sites. The particular binding sites at which hybridization occurs are detected, and one or more molecular structures within the sample are subsequently deduced.

Of great interest are molecular detection chips for gene sequencing. These chips, often referred to as DNA

chips, utilize an array of binding sites each having respective single-stranded DNA probes. A sample of single-stranded DNA fragments, referred to as target DNA, is applied to the DNA chip. The DNA fragments attach to one or more of the DNA probes by a hybridization process. By detecting which DNA probes have a DNA fragment hybridized thereto, a sequence of nucleotide bases within the DNA fragment can be determined.

To hasten the hybridization process, a local concentration of target DNA can be increased at predetermined sites using electric field enhancements. Here, each site has an electrode associated therewith for selectively generating an electric field thereby. The electric field is generated by applying an electric potential between an electrode at the site and a counter electrode at a peripheral portion of the chip. To attract DNA fragments to the site, the polarity of the electric potential is selected to generate an electric field having a polarity opposite to the charge of the DNA fragments. To de-hybridize the site, an electric field having the same polarity as the DNA fragments can be generated to repel the DNA fragments from the site.

Various approaches have been utilized to detect a hybridization event at a binding site. In one approach, a radioactive marker is attached to each of a plurality of molecules in the sample. The binding of a molecule to a molecular receptor is then detectable by detecting the radioactive marker.

Other approaches for detection utilize fluorescent labels, such as fluorophores which selectively illuminate when hybridization occurs. These fluorophores are illuminated by a pump light source external to the substrate. An external charge-coupled device (CCD) camera is utilized to detect fluorescence from the illuminated fluorophores.

An optical-detection-based DNA chip is disclosed in "Real-time detection of DNA hybridization and melting on oligonucleotide arrays by using optical wave guides", Proceedings of the National Academy of Sciences, Vol. 92, pp. 6379-6383. This DNA chip utilizes a glass substrate having a surface which defines the binding sites. The glass substrate has an end adjacent to the surface into which light is injected by an external light source. An external CCD camera is utilized to detect scatter light at the binding sites at which hybridization occurs.

Brief Description of the Drawings

The invention is pointed out with particularity in the appended claims. However, other features of the invention will become more apparent and the invention will be best understood by referring to the following detailed description in conjunction with the accompanying drawings in which:

FIG. 1 is a block diagram of an embodiment of an integrated molecular detection device in accordance with the present invention;

FIG. 2 is a schematic cross-sectional view of an embodiment of an integrated molecular detection device in accordance with the present invention;

FIG. 3 is a flow chart of an embodiment of a method of detecting hybridization of a molecule to a molecular receptor;

FIG. 4 is a schematic perspective view of a preferred embodiment of an integrated molecular detection chip in accordance with the present invention; and

FIG. 5 is a schematic cross-sectional view of the preferred embodiment of the integrated molecular detection chip.

Detailed Description of a Preferred Embodiment

Embodiments of the present invention advantageously provide an integrated molecular detection device that incorporates binding sites, a light source, and optical detection electronics onto a single chip. A preferred embodiment utilizes a micromachined glass substrate, a polymer light-emitting diode light source, and a thin-film-transistor-based optical imager to provide a fully integrated chip. By further including transparent electrodes proximate to the binding sites, the device can perform field-enhanced hybridization and de-hybridization. Embodiments of the present invention can be utilized for DNA sequencing and detection applications.

FIG. 1 is a block diagram of an embodiment of an integrated molecular detection device 10 in accordance with the present invention. The integrated molecular detection device 10 includes a substrate 12 which defines a binding site 14 for receiving a molecular receptor 16. In general, the molecular receptor 16 is selected in dependence upon the type of molecule which is to be detected. The molecular receptor 16 typically includes a biological or synthetic molecule that has a specific affinity to the molecule to be detected. For DNA sequencing and/or detection applications, the molecular receptor 16 includes at least one DNA probe having a specific base pair sequence. It is noted that embodiments of the present invention are not limited to detecting hybridization of DNA molecules. For example, embodiments of the present invention can be utilized to detect antibody-antigen binding events.

A light source 18 is integrated in the substrate 12. The light source 18 illuminates the binding site 14 through the substrate 12 to produce an optical indication of a molecule 19 hybridized or bound to the molecular receptor

16. The optical indication can be provided, for example, by a fluorophore that selectively illuminates when hybridization occurs.

An optical detector 20 is also integrated in the substrate 12. The optical detector 20 detects the optical indication through the substrate 12, and hence detects the hybridization or the binding of the molecule 19.

In a preferred embodiment, the substrate 12 is formed of glass so that the binding site 14 can be illuminated through the substrate 12, and so the optical indication can be detected through the substrate 12. In general, the substrate 12 can be formed of a substantially-transparent material to allow illumination and detection therethrough.

FIG. 2 is a schematic cross-sectional view of another embodiment of an integrated molecular detection device in accordance with the present invention. The integrated molecular detection device includes a substrate 30 which can be formed of glass. The substrate 30 defines a first side 32 (or a top side) and a second side 34 (or a reverse side). As illustrated, the first side 32 opposes the second side 34 in this embodiment.

A binding site 36 for receiving a molecular receptor 37 is defined on the first side 32 of the substrate 30. The binding site 36 can be formed by etching or micromachining a well into the substrate 30. The molecular receptor 37 is deposited into the binding site 36 using a robotic dispensing technique, a self-assembly technique, or other techniques known in the art. For DNA sequencing and/or detection applications, the molecular receptor 37 includes a chain of at least one nucleotide for detecting a molecule having a complementary chain of at least one nucleotide. Here, the molecular receptor 37 can include at least one DNA probe which selectively hybridizes with predetermined DNA molecules.

A light source 38 is incorporated on the second side 34 of the substrate 30. In a preferred embodiment, the light source 38 includes a polymer light-emitting diode fabricated on the second side 34 of the substrate 30.

The binding site 36 is illuminated by the light source 38 through the substrate 30. In other words, light generated at the second side 34 of the substrate 30 (by the light source 38) is transmitted through the substrate 30 to the binding site 36 at the first side 32. Illuminating the binding site 36 acts to illuminate an optical indicator of a molecule which has hybridized to the molecular receptor 37. Illuminating the optical indicator acts to produce an optical indication of the hybridization.

The optical indicator can be provided by a fluorophore that selectively activates when hybridization occurs. Here, the light source 38 preferably has an spectral output corresponding to absorption bands of the fluorophore. The number of fluorescent molecules can be increased by attaching multiple fluorescent molecules to a bead or like member which is attached to the molecule. It is noted, however, that embodiments of the present invention are not limited to the use of fluorescent indicators, and that other optical indicators can be utilized for the same purpose.

An optical detector 40 is incorporated on the second side 34 of the substrate 30 to detect the optical indication. The optical detector 40 can include a photodiode fabricated on the second side 34 of the substrate 30. The optical detector 40 detects the optical indication, and hence detects the hybridization of the molecule, through the substrate 30. In other words, the optical indication generated at the first side 32 of the substrate 30 is transmitted through the substrate 30 to the optical detector 40 at the second side 34.

In the embodiment of FIG. 2, the light source 38 and the optical detector 40 are located beside one another on the second side 34 of the substrate 30. To screen the optical detector 40 from light emitted by the light source 38, the integrated molecular detection device includes a filter 42 incorporated over the optical detector 40. Here, the filter 42 can include a color filter to screen out fluorescent light emanating from the light source 38.

Optionally, the integrated molecular detection device includes a transparent electrode 44 incorporated in the substrate 30 at a location proximate to the binding site 36. The transparent electrode 44 is utilized for field-assisted hybridization and de-hybridization of the molecule with the molecular receptor 37. Because of its transparency, the transparent electrode 44 allows the optical indication to be illuminated and detected at the second side 34 of the substrate 30.

FIG. 3 is a flow chart of an embodiment of a method of detecting hybridization of a molecule to a molecular receptor. Preferably, the method is utilized in conjunction with a molecular detection device as described herein. It is noted, however, that the method may also be utilized for detecting hybridization in other devices.

As indicated by block 50, the method includes a step of providing a substrate which defines a binding site for receiving the molecular receptor. The substrate can be provided within a molecular detection device, such as embodiments of the molecular detection device described herein. As described earlier, the substrate is formed of a material, such as glass, which allows a transmission of light therethrough.

As indicated by block 52, the method includes an optional step of generating an electric field using a transparent electrode proximate to the binding site. The electric field is generated to attract molecules to the

binding site to enhance hybridization to the molecular receptor.

As indicated by block 54, a step of illuminating the binding site through the substrate is performed to produce an optical indication of a molecule which has hybridized to the molecular receptor. If a transparent electrode is included, the binding site and the optical indication are illuminated through the transparent electrode. As described earlier, the binding site can be illuminated from a side of the substrate opposite to a side on which the binding site is defined. The binding site can be illuminated by a light source, such as a light-emitting diode, fabricated into the substrate.

As indicated by block 56, a step of detecting the optical indication through the substrate is performed. If a transparent electrode is included, the optical indication is detected through the transparent electrode. The optical indication can be detected from a side of the substrate opposite to the side on which the binding site is defined. The optical indication can be detected by an optical detector, such as a photodiode, fabricated on the substrate.

As indicated by block 58, the method includes an optional step of generating an electric field using the transparent electrode to de-hybridize the molecule from the molecular receptor.

FIG. 4 is a schematic perspective view of a preferred embodiment of an integrated molecular detection chip in accordance with the present invention. The integrated molecular detection chip includes a substrate 60 which defines a plurality of binding sites 62. The plurality of binding sites 62 are formed by wells 64 etched on a top surface 66 of the substrate 60. The plurality of selective binding sites 62 are arranged as a matrix in this

embodiment. In alternative embodiments, the plurality of binding sites 62 can be arranged as another type of array.

FIG. 5 is a schematic cross-sectional view of the preferred embodiment of the integrated molecular detection chip. Specific DNA receptors 70 having specific base pair sequences are deposited into the wells 64. The specific DNA receptors 70 can be deposited using techniques which include, but are not limited to, robotic dispensing techniques and self-assembly techniques.

Integrated into the substrate 60 below each of the plurality of binding sites 62 is a respective one of a plurality of optical detectors 72. Each of the plurality of optical detectors 72 includes an a-Si photodiode fabricated into a bottom surface 74 of the substrate 60. The plurality of optical detectors 72 can be matrix addressed using a-Si or poly-Si thin-film transistors to form an imaging array with a one-to-one correspondence to the binding sites 62.

Between each adjacent pair in a row of the plurality of optical detectors 72 is a respective one of a plurality of light sources 76 integrated into the substrate 60. Each of the plurality of light sources 76 includes a polymer light-emitting diode fabricated into the bottom surface 74 of the substrate 60. The plurality of light sources 76 have a spectral output corresponding to absorption bands of fluorophores used to provide the optical indication. A color filter 78 is incorporated over each of the plurality of optical detectors 72 to screen out light emanating from the plurality of light sources 76.

To speed up the hybridization and de-hybridization processes, each of the plurality of binding sites 62 has a respective one of a plurality of transparent electrodes 80 integrated in proximity thereto. The transparent electrodes 80 generate electric fields for field-enhanced hybridization and de-hybridization. The transparent

electrodes 80 are individually addressable for self-addressing and self-assembly purposes. The integrated molecular detection chip can further include a polymer membrane at each of the plurality of binding sites 62 to aid in binding molecules thereto.

In operation, appropriate DNA sequences hybridize onto selective ones of the plurality of binding sites 62 using either conventional, field-assisted, or thermally-assisted hybridization. After hybridization, unwanted sequences with only a partial binding are de-hybridized using field enhancement or thermal desorption. The plurality of light sources 76 are illuminated, and the fluorescence of each of the plurality of binding sites 62 is read by the plurality of optical detectors 72. Phase-sensitive detecting techniques can be incorporated by modulating a drive current to each of the plurality of optical detectors 72. These techniques are beneficial to enhance sensitivity of the detection.

The hybridized sites can then be detected to determine specific nucleotide sequences within the DNA sample. The molecular detection chip can then be fully de-hybridized using chemical, thermal, or field-assisted means so that the hybridization and detection process can be repeated.

Thus, there has been described herein a concept, as well as several embodiments including preferred embodiments of an integrated optical molecular detection device an a method therefor.

Because the various embodiments of the present invention integrate a binding site, a light source, and an optical detector on a single substrate, they provide a significant improvement in that a fully integrated molecular detection device is produced.

Additionally, the various embodiments of the present invention as herein-described include a transparent

electrode proximate to each binding site to provide field-assisted hybridization and de-hybridization. The transparency of the electrode allows an optical indication of binding to be both illuminated and detected through the electrode.

It will be apparent to those skilled in the art that the disclosed invention may be modified in numerous ways and may assume many embodiments other than the preferred form specifically set out and described above.

Accordingly, it is intended by the appended claims to cover all modifications of the invention which fall within the true spirit and scope of the invention.

What is claimed is:

Claims

1. An integrated molecular detection device comprising:

a substrate which defines a binding site for receiving a molecular receptor;

a light source integrated in the substrate, the light source for illuminating the binding site through the substrate to produce an optical indication of a molecule hybridized to the molecular receptor; and

an optical detector integrated in the substrate, the optical detector for detecting the optical indication through the substrate.

2. The integrated molecular detection device of claim 1 wherein the substrate is substantially transparent.

3. The integrated molecular detection device of claim 1 wherein the substrate is formed of glass.

4. The integrated molecular detection device of claim 1 wherein the substrate defines a first side on which the binding site is defined and a second side opposite to the first side on which the light source is integrated.

5. The integrated molecular detection device of claim 1 wherein the molecular receptor includes a chain of at least one nucleotide, and wherein the molecule includes a complementary chain of at least one nucleotide.

6. A method of detecting hybridization of a molecule to a molecular receptor, the method comprising the steps of:

providing a substrate which defines a binding site for receiving the molecular receptor;

illuminating the binding site with a light source integrated in the substrate, the binding site being illuminated through the substrate to produce an optical indication of a molecule hybridized to the molecular receptor; and

detecting the optical indication through the substrate by an optical detector integrated in the substrate.

7. The method of claim 6 wherein the optical indication is detected from the second side of the substrate.

8. The method of claim 7 wherein the optical indication is detected by a photodiode fabricated on the second side of the substrate.

9. The method of claim 7 further comprising the step of screening the optical detector from light which illuminates the binding site.

10. The method of claim 6 wherein the optical indication is detected through a transparent electrode proximate to the binding site.

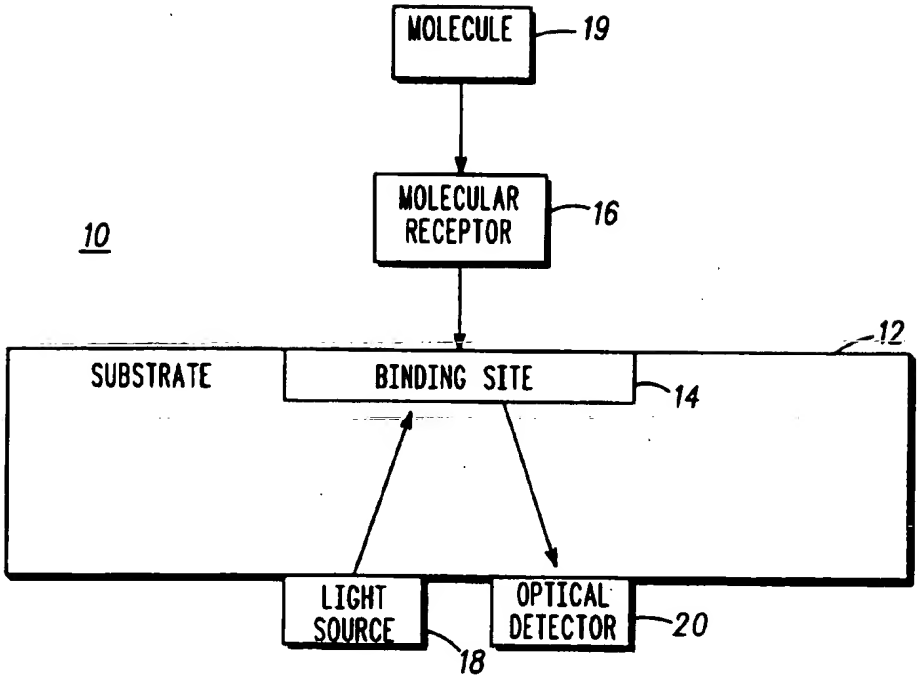
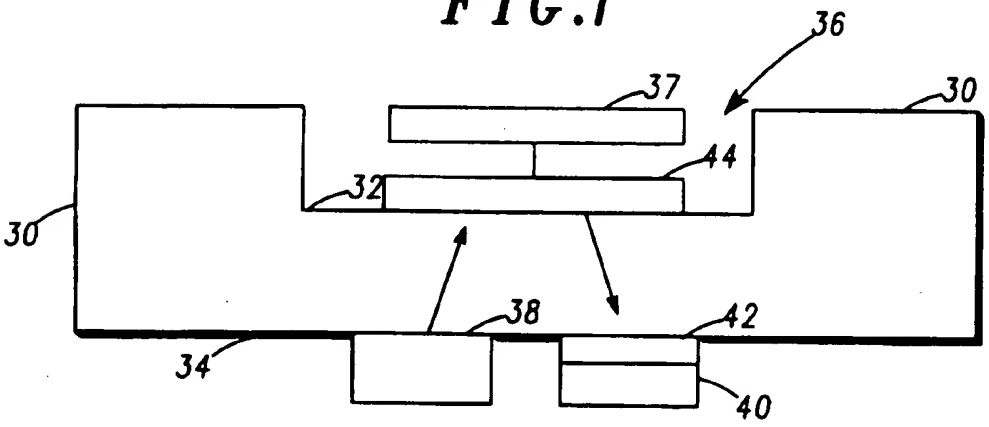

MOLECULE
19
MOLECULAR RECEPTOR
16
10
12
SUBSTRATE
BINDING SITE
14
LIGHT SOURCE
18
OPTICAL DETECTOR
20

FIG.1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34
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FIG.2

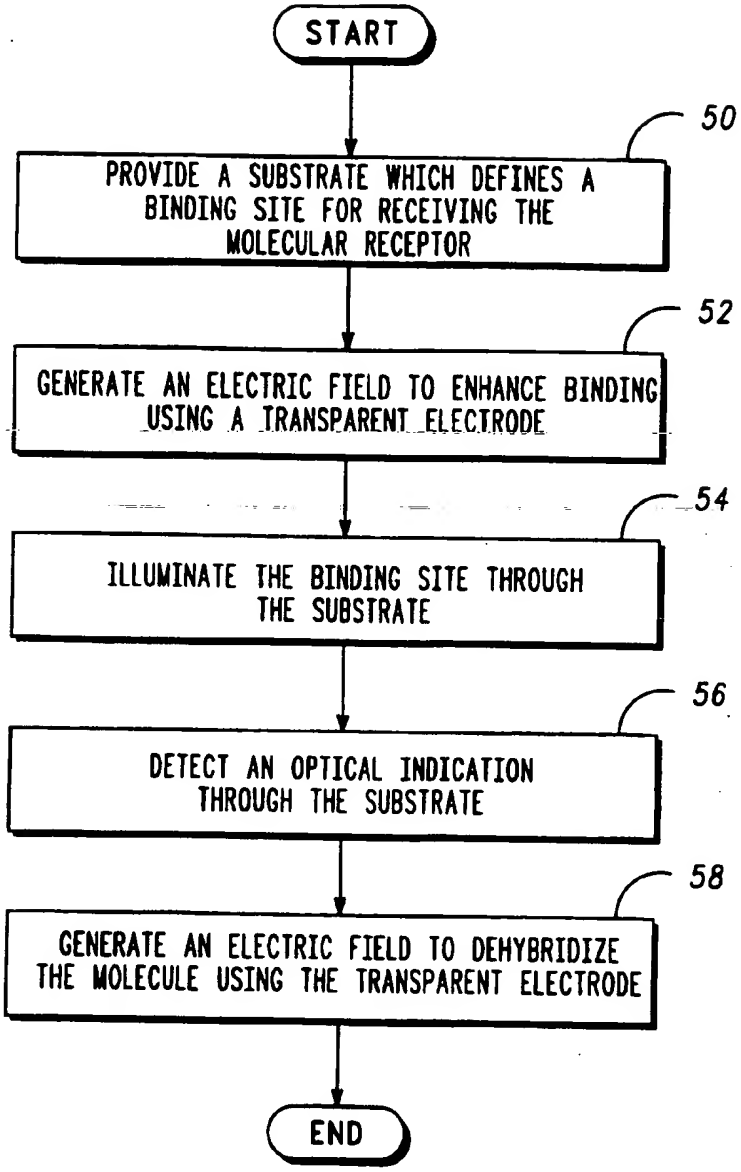
START
50
PROVIDE A SUBSTRATE WHICH DEFINES A BINDING SITE FOR RECEIVING THE MOLECULAR RECEPTOR
52
GENERATE AN ELECTRIC FIELD TO ENHANCE BINDING USING A TRANSPARENT ELECTRODE
54
ILLUMINATE THE BINDING SITE THROUGH THE SUBSTRATE
56
DETECT AN OPTICAL INDICATION THROUGH THE SUBSTRATE
58
GENERATE AN ELECTRIC FIELD TO DEHYBRIDIZE THE MOLECULE USING THE TRANSPARENT ELECTRODE
END

FIG.3

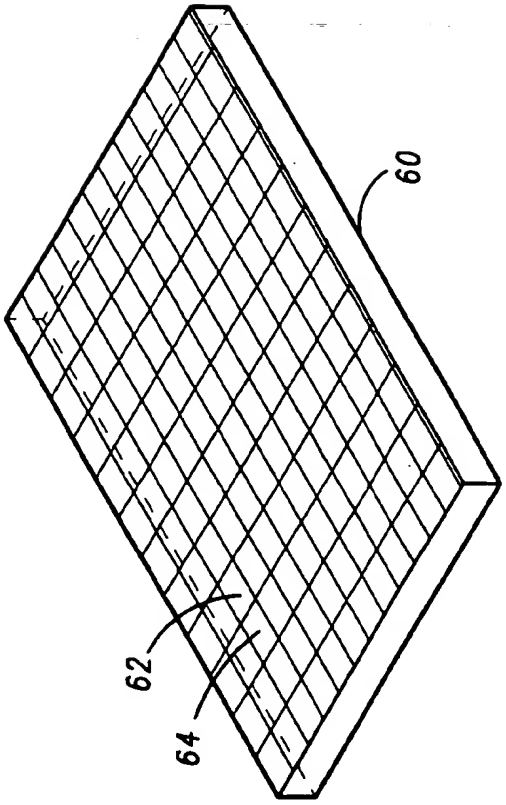

FIG.4

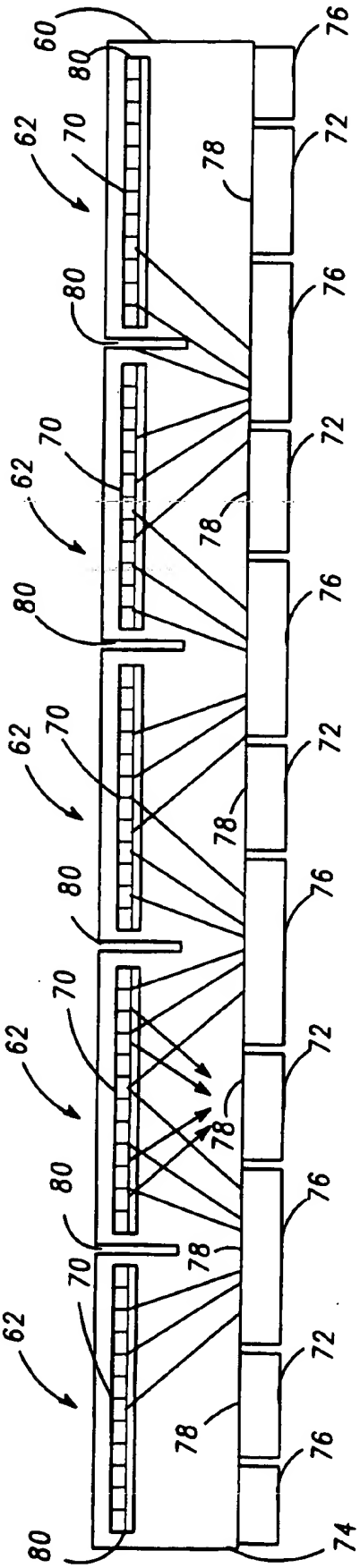

FIG.5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/05534

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6, 287.2, 288.7, 91.2; 436/ 169; 422/58, 82.05, 82.09; 204/403, 222, 400

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X ------ P, Y	US, 5,580,794 A (ALLEN) 03 December 1996, see entire document.	1-7 ---- 8-10
P, Y	US 5,527,670 A (STANLEY) 18 June 1996, see abstract.	1-10
Y	US 4,915,812 A (PARCE et al.) 10 April 1990, see entire document.	1-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Date of the actual completion of the international search 12 MAY 1997	Date of mailing of the international search report 19 JUN 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer DIANNE REES Telephone No. (703) 308-0196

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INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

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A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

435/6, 287.2, 288.7, 91.2; 436/ 169; 422/58, 82.05, 82.09; 204/403, 222, 400

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

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search terms: hybridization, hybridisation, arrays, ligand, receptor, nucleic acids, oligonucleotides, DNA, probes, polynucleotides, antibody, antigen, light source, beam, laser, detector, photodetector, electrodes, photodiode, LED, transparent electrodes, glass electrodes